Agitated depression in bipolar disorder

Francesca Serra[1], Katherine Gordon-Smith[1], Amy Perry[1], Christine Fraser[2], Arianna Di Florio[2], Nick Craddock[2], Ian Jones[2], Lisa Jones[1]

[1]Psychological Medicine, University of Worcester, UK
[2]National Centre of Mental Health, Cardiff University, UK

Corresponding author:

Professor Lisa Jones, Professor of Psychological Medicine
University of Worcester,
Henwick Grove
Worcester,
WR2 6AJ, UK
E: lisa.jones@worc.ac.uk
T: +44 (0)1905 54 2801

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Abstract

OBJECTIVES: It has been suggested that agitated depression (AD) is a common, severe feature in bipolar disorder. We aimed to estimate the prevalence of AD and investigate whether presence of AD was associated with episodic and lifetime clinical features in a large well-characterised bipolar disorder sample.

METHOD: The prevalence of agitation, based on semi-structured interview and medical case-notes, in the most severe depressive episode was estimated in 2925 individuals with DSM-IV bipolar disorder recruited into the UK Bipolar Disorder Research Network. Predictors of agitation were ascertained using symptoms within the same episode and lifetime clinical features using multivariate models.

RESULTS: 32.3% (n=946) experienced agitation during the worst depressive episode. Within the same episode, significant predictors of presence of agitation were: insomnia (OR 2.119, p<.001), poor concentration (OR 1.966, p=.027), decreased libido (OR 1.960, p<.001), suicidal ideation (OR 1.861, p<.001), slowed activity (OR 1.504, p=.001), and poor appetite (OR 1.297, p=.029). Over the lifetime illness course, co-morbid panic disorder (OR 2.000, p<.001), suicide attempt (OR 1.399, p=.007), and dysphoric mania (OR 1.354, p=.017) were significantly associated with AD.

CONCLUSIONS: Agitation accompanied bipolar depression in at least one-third of cases in our sample and was associated with concurrent somatic depressive symptoms, which are also common features of mixed manic states. Furthermore, AD in our sample was associated with lifetime experience of mixed mania, in addition to severe lifetime illness course including comorbid panic disorder and suicidal behaviour. Our results have implications for the diagnosis and treatment of agitated features in bipolar depression.

Keywords: Psychomotor agitation, bipolar disorder, somatic symptoms, panic disorder, suicide, mixed features, dysphoric mania, agitated depression.

Introduction

Agitated depression (AD) is a common clinical feature of mood disorders [1,2]. Kraepelin [3] and his followers classified AD (also called "excited depression") as a mixed state resulting from the combination of opposing polarities of symptoms: mood and thought in the depressive polarity and activity in the manic polarity [4]. Later, AD was defined through the Research Diagnostic Criteria (RDC) as a major depressive episode with psychomotor agitation [5]. More recently, Koukopoulos and colleagues [6–8] identified AD as mixed depression with two main forms: first, classic agitated depression characterized by anxiety and restlessness with motor agitation (in line with RDC criteria); and second, depression with inner psychic tension without motor agitation, dominated by racing and crowded thoughts, mood lability, spells of weeping and talkativeness. Both forms are often characterized by suicidal impulses and sometimes psychotic features. Many authors define AD as a major depressive episode with psychomotor agitation and/or the presence of excitatory symptoms [9–19] although AD still does not have an unequivocal definition [20] and is defined inconsistently across different studies in both unipolar depression and bipolar disorder.

Several studies have investigated the prevalence of AD in bipolar disorder but markedly different frequencies have been reported. In bipolar I disorder (BD-I) prevalence estimates of AD vary from 20% [19] to 50% [7], and from 32% [7] to 41% [12] in bipolar II disorder (BD-II). These studies have been performed in relatively small samples, for example, 136 BD-I participants and 417 with BD-II [7], and 216 with BD-I and 130 with BD-II [18]. They also vary substantially in the samples included and the definitions of AD [7,10,12,14,16,18,19,21,22]. For example, some studies included only patients who had not received psycho-pharmacotherapy for the episode of depression before the evaluation [12], while other studies included all patients in current treatment for a depressive episode [7,19] but used different criteria to assess AD. Maj et al.,[19] for example, used the RDC definition [5], whereas Koukopoulos et al.,[7] included patients with both of their definitions of mixed depression. Other studies have focused on patients with AD triggered by antidepressants [22]. Most of the published research on AD in bipolar disorder has focused only on current illness episodes. In unipolar depression, a retrospective approach to assess agitation in previous episodes was taken by Olgiati et al.,[11] using the operational criteria checklist (OPCRIT,[17]) , but a similar approach has not been carried out in bipolar disorder to date.

Some studies have identified demographic and lifetime clinical features associated with the presence of AD in bipolar disorder for example, female gender [7,12,19], earlier age at onset [7,12], more lifetime mixed episodes [23,24], and suicide attempt history [25,26]. In addition, within the same depressive episode in bipolar disorder AD has been associated with non-euphoric hypomanic symptoms such as distractibility and increased talkativeness [19,21], longer duration of episode [12,19], and suicidal ideation [19,21]. Therefore, AD appears to be a severe clinical feature in bipolar disorder [8,13,27]. Undetected AD could result in inappropriate treatment [10,14,24], often with dangerous outcomes [2,28]. In particular, it has been shown that antidepressant therapy in AD increases both psychomotor agitation [16,29] and other concurrent excitatory symptoms [30], and as a most serious consequence, antidepressants increase the risk of suicide in AD [9,10,23,29,31,32].

A further in-depth investigation of the prevalence and clinical correlates of AD in a large and representative sample of individuals with bipolar disorder would have clinical utility for the recognition of this serious form of depression in bipolar disorder. Therefore, the present study has three main aims: first, to evaluate the prevalence of agitation in the most severe depressive episode in a large, well characterized sample of participants with bipolar disorder; secondly, to investigate if the presence of AD is associated with other symptoms during the same depressive episode; and, thirdly, to explore whether the presence of AD is associated with lifetime clinical features.

Patients and methods

The study was part of our ongoing programme of research into the genetic and non-genetic determinants of BD and related mood disorders (Bipolar Disorder Research Network, BDRN; bdrn.org) which has UK National Health Service (NHS) Research Ethics Committee approval and local Research and Development approval in all participating NHS Trusts/Health Boards.

Participants

Participants were recruited through NHS psychiatric services, advertisements for volunteers via the BDRN website, leaflets, posters, and media coverage about the research and also through the service user-led charity, Bipolar UK.

All patients in the UK who have a diagnosis of bipolar disorder and are aged 18 years or over are eligible to take part in the BDRN research programme and enrol after giving written informed consent. The exclusion criteria are individuals who have only experienced affective illness as a consequence of alcohol or substance abuse or dependence, and/or who have only experienced affective illness as a consequence of medical illness, an organic brain disorder or medication.

Participants in the current study (N= 2925) were those from whom we had information on the presence or absence of agitated psychomotor features (defined below) during their worst depressive episode who met lifetime DSM-IV diagnostic criteria for BD-I (N= 2011) or BD-II (N= 914).

Psychiatric assessment

Lifetime clinical data for each individual were collected by a trained BDRN interviewer (research psychologist or psychiatrist) using a semi-structured psychiatric interview, the Schedules for Clinical Assessment in Neuropsychiatry (SCAN, [33]). Further lifetime clinical data were gathered from participants' psychiatric case notes. Diagnoses and clinical ratings were made using all available clinical data according to pre-specified guidelines. OPCRIT [17] was used to assess the presence/absence of individual symptoms during the most severe depressive episode. In cases where there was doubt, diagnostic and clinical ratings were made by at least two members of the research team blind to each other's ratings and consensus reached via discussion where necessary. Inter-rater reliability was formally assessed using 20 random cases. Mean kappa statistics were 0.85 for best-estimate lifetime DSM–IV diagnosis and ranged between 0.81 and 0.99 for other key clinical categorical variables, including OPCRIT ratings. Mean intra-class correlation coefficients were between 0.91 and 0.97 for key clinical continuous variables.

Agitated depression (AD) definition

We defined AD according to the OPCRIT definition, which requires the presence of excessive repetitive activity (such as restlessness, wringing of hands, pacing up and down) all usually accompanied by expression of mental anguish. In this study, agitation was rated as present/absent during the most severe episode of depression using data obtained from the SCAN interview and psychiatric case-notes. Our mean kappa statistic for the rating of AD was 0.85.

Statistical analysis

The data were analysed using SPSS version 24. The proportion of the sample with agitation present during the worst episode of depression was calculated with 95% confidence intervals (CI). The sample was dichotimised into AD-present and AD-absent, and the presence/absence of other symptoms in the same episode was compared between the two groups using chi-square tests. All symptoms that were significantly different between groups in the univariate analyses ($p<.001$) were included as predictors in a logistic regression model using the enter method with absence or presence of AD as the outcome/dependent variable. The p-value was set at $p<.001$ to account for multiple testing and minimise the likelihood of a type 1 error.

Lifetime clinical characteristics and demographics were then compared between the two groups (AD-present and AD-absent) using chi-square tests for categorical data and Mann–Whitney U tests for continuous data due to significant deviation from normal distributions. A second logistic regression analysis (enter method) was conducted. All demographic and lifetime clinical features significantly different in the univariate analyses ($p<.001$) were included as predictors with absence or presence of agitated features as the outcome/dependent variable.

Results

Prevalence of agitated depression

Almost a third of the episodes of depression met our definition of agitated depression, with 32.3% of the sample (946/2925) experiencing agitation during the most severe episode of depression (95% CI: 30.6% - 34.0%).

Concurrent depressive episode symptoms according to the presence/absence of agitation

As reported in Table 1 and shown in Figure 1, compared to individuals without agitation in their most severe episode of depression, significantly more individuals with agitation present experienced the following seven depressive symptoms during the same episode ($p<0.001$): i) suicidal ideation, ii) excessive self-reproach, iii) poor concentration, iv) slowed activity, v) poor appetite, vi) insomnia, and vii) diminished libido. Conversely, significantly fewer individuals with agitated features present experienced excessive sleep in the same episode.

- INSERT TABLE 1 HERE –

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These eight symptoms were included in the logistic regression analysis. The symptoms that significantly predicted the presence of concurrent agitated features within the worst episode of depression were: **insomnia** (OR 2.119, 95% C.I: 1.649 – 2.723, p<.001); **poor concentration** (OR 1.966, 95% C.I: 1.079 – 3.580, p=.027); **diminished libido** (OR 1.960, 95% C.I: 1.481 – 2.593, p<.001); **suicidal ideation** (OR 1.861, 95% C.I: 1.323 – 2.618, p<.001); **slowed activity** (OR 1.504, 95% C.I: 1.173 – 1.927, p=.001); and, **poor appetite** (OR 1.297, 95% C.I: 1.027 – 1.639, p=.029). This model explained 12.5% of the variance and correctly classified 68.5% of participants as having agitated features or not.

Demographic and lifetime clinical features according to the presence/absence of AD

There was no significant difference in the proportion of males and females between the AD-present and AD-absent groups, and the age of interview was similar in both groups (see Table 2). There were significantly fewer participants who had completed higher education (educated to at least Bachelor degree level) in the AD-present group (33.8% v 42.7%).

Compared to the AD-absent individuals, individuals with AD-present had significantly:

- Higher rate of BD-II (35.5% vs 29.2%, p<.001)
- Higher rate of lifetime alcohol misuse (53.1% vs. 44.4%, p<.001)
- Higher rate of lifetime panic disorder (78.0% vs. 59.0%, p<.001)
- Higher rate of lifetime dysphoric mania (45.6% vs. 33.8%, p<.001)
- Higher rate of lifetime ever suicide attempt (41.3% vs. 32.8%, p<.001)
- Higher rate of rapid cycling over the lifetime illness course (41.9% vs. 33.4%, p<.001)
- Younger age at illness onset (19 vs. 20 years, p<.001)

- INSERT TABLE 2 HERE –

The demographic and lifetime clinical characteristics that were significantly more common or greater in the AD-present group (p<.001) were included in the logistic regression analysis. The lifetime clinical characteristics that significantly predicted the presence of AD were: **lifetime**

occurrence of panic disorder (OR 2.000, 95% C.I: 1.527 – 2.618, p<.001); **occurrence of at least one suicide attempt** (OR 1.399, 95% C.I: 1.094 – 1.790, p=.007; and, **lifetime occurrence of dysphoric mania** (OR 1.354, 95% C.I: 1.055 – 1.737, p=.017). This model explained 8.5% of the variance and correctly classified 68% of participants as AD-present/absent. We excluded rapid cycling from the initial regression due to the high number of cases where a definite rating of the absence of rapid cycling could not be made (our definition requires at least 7 years from the onset of illness and/or more than 3 affective episodes to give a definite rating of presence/absence), which would have reduced the size of the whole sample in the regression model. However, we repeated the regression with a reduced sample size including the rapid cycling variable and the significant predictors were the same.

Discussion

This study is carried out in the largest sample of individuals with bipolar disorder to date. We found that AD, defined as psychomotor agitation within the most severe episode of depression, was present in almost one-third (32.3%) of individuals in our sample. Although we found a higher prevalence of AD in BD-II (36.8 %) than BD-I (30.3 %), lifetime diagnosis was not a significant predictor of the presence of AD after controlling for other clinical and socio-demographic features. Previous research is not consistent about the prevalence of AD in bipolar disorder [20] probably due to the various definitions of AD employed across different studies, including the more extended definition of depression with mixed features [34], in addition to heterogeneity between samples. However, Judd et al.,[16] found a prevalence of 39%, similar to our finding, specifically for psychomotor agitation in their bipolar disorder sample. When the prevalence of AD has been compared between unipolar depressive disorder and bipolar disorder the results have systematically highlighted a higher prevalence of AD in bipolar disorder [2]. Interestingly, Olgiati et al., [11], using OPCRIT to define AD as we did, found a prevalence of 19% in unipolar depressive disorder, so approximately 1 in 5 compared to our rate of approximately 1 in 3 in bipolar disorder. Our data strengthen the evidence that agitated activity is a significant feature of bipolar depression.

While much of the previous research has focused on the association between agitated features and manic symptoms within the same depressive episode [14,28,34], little is known about concurrent depressive symptoms associated with AD. From our analysis of a large well-characterised bipolar

disorder sample emerges an association between AD and somatic symptoms of depression, specifically decreased libido, insomnia, poor appetite, and slowed activity, even after controlling for other correlates of AD. Moreover, we found AD was associated with poor concentration and suicidal ideation. Consistently, previous research has demonstrated that patients experiencing mixed depressive episodes are significantly more likely to have suicidal ideation and suicidal behaviour [10,26,35], poor concentration [11,14,19], poor appetite [11] and insomnia [2,7,10]. Intriguingly, these symptoms are also typical symptoms of a mixed manic episode [23,28,36]. Previous literature is not consistent regarding the association that we found between concurrent agitated and slowed activity. Maj et al., [19] showed slowed activity is more common in non-agitated episodes of depression than AD episodes, while in line with our data, Angst et al., [10] reported that both agitated activity and slowed activity are often part of the same depressive episode. To the best of our knowledge, ours is the first study to demonstrate an association between decreased libido and agitated activity. Our within-episode findings could suggest that the presence of agitated activity in bipolar depression represents a clinical subtype of bipolar depression with a predominant biological aetiology given the association with other physical depressive symptoms (poor appetite, slowed activity, diminished libido, insomnia). Further research is needed to examine symptoms of both manic and depressive polarity in relation to agitation within episodes of bipolar depression. Unfortunately we did not have data on specific manic/hypomanic symptoms concurrent with the depressive episode to allow us to examine this.

We found that individuals with bipolar disorder and comorbid lifetime panic disorder were twice as likely to experience AD compared to individuals without a history of panic disorder. The combination of agitated activity and panic may not be unexpected due to our definition of AD where the aspect of psychomotor activation is paramount. Historically, Kraepelin [3] underlined the correlation between agitated depressive states and anxiety. Some authors suggested that both agitated depression and panic anxiety may be associated with high serum catecholamine level [37]. Recently this issue has not received great attention, and our study is the first that shows a strong association between AD and panic, suggesting that both clinical manifestations could implicate similar biological mechanisms, however this matter deserves further study to understand the mechanisms of the association.

Our data show an association between AD and lifetime dysphoric mania episodes. Our definition of dysphoric mania is an episode of mania in which the predominant mood is characterized by unease or mental discomfort (including low mood), which is consistent with mixed state definitions [3,38]. Swann et al., [39] examined the clinical manifestations of AD (according to RDC) and dysphoric mania, suggesting they are two forms of mixed state both strongly associated with dysphoric mood and agitation. Similar to our results they found that AD was most strongly associated with somatic symptoms and anxiety, while dysphoric mania was associated with manic thought and hostility. Our data suggest that individuals with bipolar disorder who experience AD are also more likely to have mixed manic episodes in their lifetime, which is in line with previous research that has identified a subtype of bipolar patients characterized by a clinical course of mixed episodes [24,28,32]. Our finding that agitated activity in bipolar depression is associated with concurrent depressive symptoms that have been shown to be common in mixed manic episodes [23,36] (poor concentration, poor appetite, insomnia, and suicide behaviour) in other samples is of relevance here, and should be examined within the same sample. We do not have detailed symptom data for individual mixed manic episodes to be able to examine this in our sample.

It has previously been shown that individuals with bipolar disorder who experience mixed states have a more severe illness course with high risk of suicide [20,28]. Rihmer and colleagues [25] reported a high prevalence of depressive mixed states among suicide attempters, and in particular psychomotor agitation is known to be a significant risk factor for suicide [26]. Consistent with previous research, we found an association between AD and lifetime suicide attempt. Our finding within a large sample highlights the need for the detection of agitated features in both past and current episodes of depression among individuals with bipolar disorder which could enable clinicians to identify those at elevated risk of future suicide attempts.

Our data have clinical relevance for the diagnosis and treatment of AD in bipolar disorder. Our finding that specific concurrent depressive symptoms may be associated with psychomotor agitation could be useful to identify the manifestation of AD and then target treatment accordingly. At the same time, the correlation of specific lifetime clinical features with AD suggests, in agreement with previous empirical evidence, that particular care is needed in the pharmacological treatment of bipolar depression symptomatology [30,40,41]. For example, depressive episodes with panic comorbidity are often treated with antidepressants [42], however, the treatment should be

closely monitored in order to identify possible psychomotor agitation since such symptomatology can worsen with antidepressants [8,16] and, at worst, increase risk of suicide [30,35].
Moreover, individuals who experience both AD and dysphoric mania during their lifetime could belong to a subtype of bipolar disorder characterized by mixed episodes with a high risk of suicide attempt for which antidepressant medication is not recommended [23,24].
Thus, the recognition of psychomotor agitation during bipolar depression may be essential for the outcome of the episode and for the overall course of illness.
Notably, the presence of AD in unipolar depressive disorder has been shown to be associated with markers of bipolarity [43,44,45] (subthreshold hypomanic symptoms[9,11] and family history of bipolar disorder [9,46]), therefore, as suggested by Rihmer et al. [47], future research should aim to differentiate patients with "pure" unipolar depression from patients with "mixed" or "agitated" depression when conducting, for example, clinical trials on antidepressant therapy efficacy or genome wide association studies (GWAS) [48].

A potential limitation of our study is the conceptualisation of the term agitated depression. There is not a unanimous definition of AD in the literature to date [1,20] and the existence of different definitions may affect the estimates of AD prevalence and correlated variables across different studies. We used the OPCRIT definition of AD [17], which is consistent with both the original Kraepelin definition of AD in which mood and ideation are in the negative polarity and activity in a positive polarity [4] and with RDC criteria for AD [5]. However, our definition of AD focuses specifically on agitated activity and is not compatible with the more extended definition of mixed depression that includes agitated thoughts with concurrent manic symptoms in the absence of motor agitation [34]. We did not have data on other specific manic/hypomanic symptoms concurrent with the depressive episode, and thus could not extend our definition. Furthermore, we did not collect detailed information on medication taking during the specific episode of AD, so were unable to examine the relationship between medication and agitation. In addition, we only had detailed symptom ratings for the worst-ever episode of depression for each participant and it is possible that in some cases agitated features were only present in other less severe episodes. Therefore our prevalence estimate of AD in bipolar disorder is at the lower bound, and the true prevalence is likely to be higher. Moreover, our study design only allows us to detect associations between AD and other clinical features, without a longitudinal design we cannot infer temporality and causality between agitated features and other clinical characteristics of the sample.

Nevertheless, this study is the largest to date offering an estimate of the prevalence of AD in individuals with a lifetime diagnosis of bipolar disorder and a clear picture of the associations between AD and other episodic and lifetime clinical features. It comprehensively brings together both novel and previously explored associations of episode and lifetime features with AD using systematic and comprehensive methods of clinical assessment exercised by trained researchers with a high degree of inter-rater reliability.

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TABLE 1: Symptoms present/absent in the most severe episode of depression by the presence/absence of agitation

OPCRIT SYMPTOMS, N (%)	AGITATION PRESENT (N=946)	AGITATION ABSENT (N=1979)	χ^2 (p)
Loss of pleasure			
Present	891 (98.5%)	1859 (96.3%)	9.974
Absent	14 (1.5%)	72 (3.7%)	(.002)
Diurnal variation (mood worse mornings)			
Present	458 (52.6%)	935 (49.6%)	2.165
Absent	412 (47.4%)	949 (50.4%)	(.141)
Suicidal ideation			
Present	787 (87.7%)	1475 (77.2%)	**43.105**
Absent	110 (12.3%)	435 (22.8%)	**(<.001)**
Excessive self-reproach			
Present	842 (94.5%)	1682 (90.5%)	**12.916**
Absent	49 (5.5%)	177 (9.5%)	**(<.001)**
Poor concentration			
Present	865 (97.5%)	1697 (91.3%)	**37.330**
Absent	22 (2.5%)	162 (8.7%)	**(<.001)**
Slowed activity			
Present	567 (69.9%)	1021 (58.9%)	**28.316**
Absent	244 (30.1%)	711 (41.1%)	**(<.001)**
Loss of energy			
Present	875 (96.3%)	1809 (94.9%)	2.524
Absent	34 (3.7%)	97 (5.1%)	(.112)
Poor appetite			
Present	570 (65.6%)	952 (52.2%)	**43.189**
Absent	299 (34.4%)	873 (47.8%)	**(<.001)**
Increased appetite			
Present	233 (27.6%)	480 (26.6%)	.282
Absent	612 (72.4%)	1325 (74.4%)	(.596)
Insomnia			
Present	538 (77.3%)	863 (55.2%)	**100.020**
Absent	158 (22.7%)	701 (44.8%)	**(<.001)**
Excessive sleep			
Present	377 (46.1%)	928 (53.6%)	**12.283**
Absent	440 (53.9%)	804 (46.4%)	**(<.001)**
Diminished libido			
Present	644 (83.0%)	1188 (70.8%)	**41.414**
Absent	132 (17.0%)	489 (29.2%)	**(<.001)**

TABLE 2. Demographic and lifetime clinical features by presence/absence of agitated depression

DEMOGRAPHIC CHARACTERISTICS	AGITATED DEPRESSION		
	PRESENT(N=946)	**ABSENT**(N=1979)	
Sex, n (%)			
Male	279 (29.5%)	639 (32.3%)	χ^2=2.324
Famale	667 (70.5%)	1340 (67.7%)	p=.127
Educational Attainment, n (%)			
Higher education absent	584 (66.2%)	1070 (57.3%)	**χ^2=19.943**
Higher education present	298 (33.8%)	798 (42.7%)	**p<.001**
Age at interview in years			
Median	46	46	Z=-.283
Interquartile range (IQR)	17(18-83)	19(18-79)	p=.777
LIFETIME CLINICAL FEATURES			
DSM-IV diagnosis, n (%)			
BPI	610 (64.5%)	1401 (70.8%)	**χ^2=11.867**
BPII	336 (35.5%)	578 (29.2%)	**p<.001**
Cannabinoids regular use, n (%)			
Present	666 (74.0%)	1482 (77.6%)	χ^2=4.382
Absent	234 (26.0%)	428 (22.4%)	p=.036
Alcohol misuse †, n (%)			
Present	474 (53.1%)	827 (44.4%)	**χ^2=18.627**
Absent	418 (46.9%)	1037 (55.6%)	**p<.001**
Dysphoric mania ‡, n (%)			
Present	349 (45.6%)	556 (33.8%)	**χ^2=31.075**
Absent	417 (54.4%)	1091 (66.2%)	**p<.001**
Suicide attempt, n (%)			
Present	381 (41.3%)	640 (32.8%)	**χ^2=19.900**
Absent	542 (58.7%)	1314 (67.2%)	**p<.001**
Panic disorder, n (%)			
Present	482 (78.0%)	652 (59.0%)	**χ^2=63.864**
Absent	136 (22.0%)	454 (41.0%)	**p<.001**
Psychosis, n (%)			
Present	463 (58.8%)	962 (56.7%)	χ^2 =.941
Absent	325 (41.2%)	735 (43.3%)	p=.332
Rapid Cycling §, n (%)			
Present	247 (41.9%)	468 (33.4%)	**χ^2=13.030**
Absent	342 (58.1%)	932 (66.6%)	**p<.001**
Age at illness onset in years ¶, n (%)			
Median	19	20	**Z=3.582**
Interquartile range (IQR)	10(4-64)	11(4-65)	**p<.001**
Family history of bipolar disorder ¥, n (%)			
Present	354 (53.0%)	692 (49.9%)	χ^2 =1.696
Absent	314 (47.0%)	694 (50.1%)	p=.193

†**Alcohol misuse:** defined as >14 units in women and >21 units in men per week with related impairment.

‡ **Dysphoric mania**: defined as manic episode in which the predominant state was dysphoria, i.e., An unpleasant state characterised by unease or mental discomfort including low mood.

§**Rapid cycling:** defined as 4 or more affective episodes in one 12 month period.

¶**Age at illness onset:** defined as age at which symptoms of affective disorder first caused significant impairment.

¥ **Family history of bipolar disorder:** defined as at least one first- or second-degree relative with bipolar I disorder, bipolar II disorder, or schizoaffective disorder – bipolar type.

Figure 1: Frequency of symptoms present in the worst episode of depression by the presence/absence of agitation